Modeling Variability and Uncertainty in Risk Assessment: a Case Study of *Salmonella* in Low $a_w$ Foods and its Use in Decision Making

Organized by: Microbial Modelling and Risk Analysis PDG

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Facilitated Discussion

- Questions should be submitted via the Text Chat section at the bottom of the screen.
- Q&A’s to be held at the end of presentation
Modeling Variability and Uncertainty in Risk Assessment: a Case Study of *Salmonella* in Low $a_w$ Foods and its Use in Decision Making

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Jenny Scott

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Before we start…

The information and conclusions presented in this webinar do not necessarily represent new Agency policy nor do they imply an imminent change in existing policy.
Outline of today’s webinar

• Introduction
• *Salmonella* in low water activity foods
  – Prevalence and levels of contamination
  – Survival
  – Predictive modelling
• Modelling uncertainty and variability when assessing risk
  – The inference process
  – Simulation
  – Challenges
• Variability and uncertainty in risk management
  – Usefulness when making decisions
Variability and Uncertainty

Variability

Heterogeneity

- Not reduced by additional data
- May be better characterized
- Growth, inactivation, serving size, ...

Uncertainty

- Reduced by additional data
- Dose response, storage times, serving size, ...

In many cases, factors are both variable and uncertain
Quantitative Microbial Risk Assessment

Assess the risk of illness from consumption of a product by a population

Hazard Identification
Describes hazard/host/food/food characteristics that impact the risk

Exposure Assessment
How often is the hazard ingested?
How many are ingested?

Hazard Characterization
For a given ingested dose, how likely is the adverse effect?

Risk Characterization
What is the probability of occurrence of the adverse effect? What is the impact of interventions to change the risk?

- Initial contamination
- Initial concentration
- Process characteristics
- Storage conditions
- Serving size
- Dose
- Dose Response
- Etc.
Quantitative Microbial Risk Assessment: An example

Understanding extremes can help risk management


Variability and Uncertainty in Risk Assessment

DM = Deli meats; PM = Pasteurized Fluid Milk; HFD = High Fat and Other Dairy Products; FNR = Frankfurters (not reheated); SUC = Soft Unripened Cheese; P = Pâté and Meat Spreads; CR = Cooked Ready-To-Eat Crustaceans; UM = Unpasteurized Fluid Milk; SS = Smoked Seafood; F = Fruits; FR = Frankfurters (reheated); V = Vegetables; DFS = Dry/Semi-dry Fermented Sausages; FSC = Fresh Soft Cheese; SSC = Semi-soft Cheese; SRC = Soft Ripened Cheese; DS = Deli-type Salads; RS = Raw Seafood; PF = Preserved Fish; IC = Ice Cream and Frozen Dairy Products; PC = Processed Cheese; CD = Cultured Milk Products; HC = Hard Cheese.
Salmonella in low $a_w$ foods
Salmonella in low $a_w$ foods: Contamination level

- Prevalence
- Contamination level
  - Survival
  - Growth
  - Dose-Response
- Consumption

Hazard Identification
Describes hazard/host/food/food characteristics that impact the risk

Exposure Assessment
How often is the hazard ingested?
How many are ingested?

Hazard Characterization
For a given ingested dose, how likely is the adverse effect?

Risk Characterization
What is the probability of occurrence of the adverse effect? What is the impact of interventions to change the risk?

- Variability and uncertainty
- From year to year, from lot to lot, intra lot
Salmonella in sesame seeds; Variability

95% confidence limits for observed values

Observed between shipment distribution
Salmonella in almonds; Variability

Intra Lot: Poisson distribution
Inter Lot: Log normal distribution
Year to year: same mean of the log, varying standard deviation

Probability density functions of Salmonella contamination as predicted by the model.

Data: Unpublished data submitted to Federal Docket through Federal Register Notice FDA-2013_N-0747
Salmonella in low $a_w$ foods - Survival Data

### Hazard Identification
*Describes hazard/host/food/food characteristics that impact the risk*

### Exposure Assessment
*How often is the hazard ingested? How many are ingested?*

### Hazard Characterization
*For a given ingested dose, how likely is the adverse effect?*

### Risk Characterization
*What is the probability of occurrence of the adverse effect? What is the impact of interventions to change the risk?*

**Variability and Uncertainty in survival:**
- Experimental conditions
- Strain
- Temperature
- $a_w$
- Food composition
- Survival model parameters

**Questions for Survival**
- Prevalence
- Contamination level
- Growth
- Dose-Response
- Consumption
Salmonella spp. survival at various T and $a_w$ on whey protein powder

21 °C

50 °C

How do we model this variability and uncertainty for use in risk assessment?
Step 1: Inference process from data

Specific Data

Variability

- Frequentist model: “Two passes” mixed models
- Bayesian hierarchical models

Uncertainty

Step 2: Risk assessment process

Variability

- Uncertainty analysis
- Second order Monte Carlo simulations

Uncertainty

(One pass: Bayesian model) (see Albert et al., 2008)
Inference: Frequentist

- Two passes (example: inactivation data)
  - Obtain data from representative situations (strain, stress, ...)
  - Model individual datasets for each strains/conditions → get a set of parameters
  - Parameter variability distribution derived from this set of model parameters

\[
\text{Slope} \sim \text{Normal}(-0.0078388, 0.00178)
\]
• One pass, directly from data
  – Mixed (linear or non linear) models are ways to consider population variability.

• Example: (log-)linear inactivation curves obtained from a set of strains $i$
  \[
  y_{ij} = \alpha_{ij} + \gamma_i x + \varepsilon_{ij},
  \]
  \[
  \gamma_i \sim \text{Normal}(\beta, \sigma_1^2)
  \]
  \[
  \varepsilon \sim \text{Normal}(0, \sigma_2^2)
  \]
  (rather than $y_{ij} = \alpha_{ij} + \beta x + \varepsilon_{ij}$),

• The (log-)decrease varies from one strain to the other

Inference: Frequentist
Variability from replicate to replicate

\[ \delta_i \sim \text{Normal}(171, 4^2) \]
Uncertainty

- Asymptotic distribution of estimators
  - Usually: normal
  - Difficulty to consider correlations
  - (sample size?)

- Bootstrap
  - Pros: set of parameters that can be incorporated in the risk assessment model
Inference: Bayesian

\[ N_t = N_0 - \left( \frac{t}{\delta} \right)^p \]

Media: m

Product: p

Replicates: r

Point: t

\[ N_0, m \]

\[ \sigma_1 \]

\[ \sigma_2 \]

\[ \delta_p \]

\[ \delta_{p,r} \]

\[ p_p \]
Issue: Ad-hoc experimental design

• Variability
  – From population to population (strain-to-strain)
  – From day-to-day
  – From cell-to-cell within a population

• Need specific experimental design
  – No “cocktail” of strains, no “average” over replicates
  – Control of strain-to-strain, day-to-day conditions
  – See, e.g. den Besten et al., 2016
    • Experimental < Reproduction < Strain = Growth History = Population for *L. monocytogenes* inactivation
• Ad-Hoc data
  – Specific experimental design

• Literature data (meta analysis)
  – Representative strains?
  – How to consider lab-to-lab variability?
Example: *Salmonella* survival on tree nuts
Step 1: Inference process from data

- Specific Data
- Variability
  - Frequentist model: “Two passes” mixed models
  - Bayesian hierarchical models

Step 2: Risk assessment process

- Variability
  - Uncertainty analysis
  - Second order Monte Carlo simulations

Uncertainty

(One pass: Bayesian model)
Test alternative values for uncertain parameters / model

- **Baseline**
- **Alternative #1: little impact**
- **Alternative #2: high impact**
Two-Dimensional (or Second Order) Monte-Carlo simulation

• Principle
  – Separation of the parameters according to the meaning of their dispersion
    • Variable parameters
      – Example: Portion Size (from individual to individual), Distribution of the contamination | mean contamination (from year to year)
    • Uncertain parameters
      – Example: Mean of the number of bacteria / 100g for a given year

  – Model Integration using Two Embedded Monte-Carlo Simulations
    • A Variability modeling embedded in an Uncertainty modeling
Second-Order Monte Carlo Simulation

Uncertain parameter $X$ (example: mean log$_{10}$ decrease / week)
  Fixed to a given random sample issued from the uncertainty distribution

QRA Model (variable parameters)

Mean: 2.6

Mean: 3.2

Uncertain parameter $X$ (example: mean log$_{10}$ decrease / week)
  Fixed to a given random sample issued from the uncertainty distribution

$N_u$ times...

$N_u$ Means: median 3.3, 2.5 and 97.5$^{th}$ percentiles [.2, 6.9]
In practice

- Separation of uncertainty and variability is not explicitly considered in most MC software used in QMRA

- Can be done in classical MC software using large matrices or use other tools

- 2D-MC simulation to be implemented in FDA-iRISK® 3.0

- R package mc2d “Ease the development of MC and 2D-MC in R”
  - (you specify if the distributions represent Uncertainty or Variability, then mc2d do the math for you)

Variability cumulative distribution plots of the output of an E. coli model in ground beef model
Results
• In this talk, we considered only data uncertainty within a given model
• Need to consider other sources of uncertainty
  – Scenario uncertainty
  – Model uncertainty
• May be much more important than the data uncertainty
Salmonella in almonds

- The “outbreak situation” is not simply an extreme of the “usual situation”.
- Needed to consider separately “usual situation” and “outbreak situation”, as was done in this paper

Conclusions

• Don’t mix variability and uncertainty
  – Easiest way: consider variability only and test uncertainty for some major parameters
  – More complex methods available
  – Need carefully designed data collection for risk assessment purpose to consider proper variability

• Don’t forget Scenario and Model uncertainty
  – Need to model “exceptional events” that are not the extreme of the usual distribution
    • May lead your whole risk
    • Frequency? Magnitude?
How can we use the modeled variability and uncertainty for decision making?
Risk Management

IDEALLY...

1. DATA AVAILABLE

2. RISK ASSESSED WITH UNCERTAINTY AND VARIABILITY

3. INFLUENCING FACTORS DETERMINED

4. DECISION MADE

SITUATION RARELY IDEAL, ASSUMPTIONS HAVE TO BE MADE
How to make a decision?

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<th>Estimated mean number of cases</th>
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Overall challenges in considering uncertainty and variability in risk analysis

• Risk assessors
  – Complicated process/ Not well understood
  – Feasibility
  – Lack of “easy-to-use” tools

• Risk managers
  – More difficult to handle
  – The uncertainty may be considered as “too large”
  – How to “draw a line”? 

• Risk communication
  – More difficult to communicate
  • “So you are not certain?”
References used

- den Besten, H. M., D. C. Aryani, K. I. Metselaar and M. H. Zwietering (2016). "Microbial variability in growth and heat resistance of a pathogen and a spoiler: All variabilities are equal but some are more equal than others." Int J Food Microbiol.
- Food and Drug Administration / Food Safety and Inspection Service (2003). Quantitative assessment of relative risk to public health from foodborne Listeria monocytogenes among selected categories of ready-to-eat foods, Food and Drug Administration, United States Department of Agriculture, Centers for Disease Control and Prevention: 541. [http://www.fda.gov/Food/FoodScienceResearch/RiskSafetyAssessment/ucm183966.htm](http://www.fda.gov/Food/FoodScienceResearch/RiskSafetyAssessment/ucm183966.htm)

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